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Possibilities to breed for resistance to nematode parasite infections in small ruminants in tropical production systems

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*Gastrointestinal nematode parasitism is the most important disease affecting livestock production systems in developing countries, particularly small ruminant production systems. Of particular importance are infections with the strongyle *Haemonchus contortus*. Integrated disease control strategies are required, including improved management, nutrition and wise use of anthelmintic chemicals. Increasingly, selection of sheep or goats for improved nematode resistance is viewed as a valuable option to complement other control measures. Breeding for resistance is possible because of the existence of extensive genetic variation in resistance, both within and between breeds of sheep and goats. Such breeding schemes are most likely to be based on choice of appropriate breeds adapted to the local environmental conditions, followed by phenotypic selection for resistance. Goal and selection objective traits are likely to include performance (e.g. growth rate) under conditions of parasite challenge, faecal egg count (FEC) and measures of anaemia. With current technologies, genetic markers are likely to be too expensive and logistically difficult to incorporate into breeding schemes in tropical or developing countries. Genotype by environment interactions may be expected, particularly when comparing animals in environments that differ in the extent of parasite challenge or differ in the quality of available nutrition. However, there is no reason to expect antagonistic genetic relationships between performance and resistance, and selection indices should be readily constructed that improve both performance and resistance. If FEC is decreased, then pasture contamination should also decrease, leading to additional benefits for all sheep grazing the same pasture. Finally, breeding for nematode resistance should lead to lasting and sustained improvements in resistance or tolerance. There is no empirical evidence to suggest that nematodes will evolve rapidly in response to resistant hosts, and mathematical models based on genetic and biological principles also suggest that resistance should be sustainable.*

Keywords: sheep, goats, nematodes, genetics, breeding

Implications

Breeding tropical sheep or goats for enhanced resistance to nematode parasites should lead to sustained improvements in animal health and performance. It is recommended that selection is based on phenotypic measurements such as performance under conditions of nematode challenge, faecal egg count and measures of anaemia such as packed cell volume or Famacha[®] score. With currently available technologies, it is unlikely that genetic markers will make a large contribution to such breeding programmes.

Introduction: context for breeding for nematode resistance

Tropical livestock production systems, particularly those for small ruminants, are diverse and influenced substantially by

both genetic and environmental factors, and their interaction. Within such production systems, animal adaptation to the environmental circumstance is one of the key factors affecting the success of the production system. Identifiable factors impacting on animal adaptation include heat tolerance (Silanikove, 2000; Thornton *et al.*, 2009), ability to cope with often poor-quality forages and ability to cope with numerous endemic disease challenges. This paper addresses the ability of sheep and goats to cope with disease, specifically disease caused by gastrointestinal nematode parasites, the most important of which is the strongyle parasite *Haemonchus contortus*.

Disease has major impacts on tropical livestock production systems, including production losses, uncertain family food security and loss of income, and some diseases and the strategies used to manage them directly impact human health. In market-oriented terms, the costs of disease are estimated as 35% to 50% of turnover within the livestock

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sector in the developing world. All animal production systems are subjected to infectious disease and the consequent production losses. Disease also poses threats across species barriers. Firstly, several animal infections pose zoonotic threats to human health, and diseases in one species may act as reservoirs for infections in other species. Furthermore, uncertainties in terms of threats to food security and instability of livestock production systems are a further impact of animal disease.

Options for the management of infectious disease include vaccination, chemotherapy, improved management including better nutrition, diagnosis and removal of infected animals, and genetic change of the host. Each of these options can contribute to solving the problems caused by disease; however, often none on their own is sufficient to control the disease problem. Furthermore, disease management options may interact; the use of one option may enhance or diminish the effectiveness of another. A detailed assessment of the interaction of various disease control measures for the case of nematode infections in sheep is given by Jackson *et al.* (2009).

Disease management may also break down, for example, the infectious pathogen or parasite may evolve to avoid the control measure. Strategies based on a single approach are the most vulnerable, whereas those based on multiple approaches are inherently more resilient and stable. For example, integrated pest management, a strategy that aims to combine several approaches, is well established in the management of plant diseases with the concepts easily transferable to livestock (Campbell, 1994). In the context of nematode infections, anthelmintic resistance, the evolution of parasites to become resistant to the chemicals used for their control, is a major concern worldwide (Waller, 2003).

This paper focuses on gastrointestinal nematode parasitism, because of its ubiquitous importance to grazing ruminants. In a study considering diseases impacting upon livestock producers in developing countries, in which diseases were ranked on their economic impact, human health impact, animal welfare and implications on international trade, Perry *et al.* (2002) concluded that helminthosis (i.e. diseases including those caused by nematode parasites) was the most important disease in sheep and goat production systems. In fact, from Perry's ranking system, helminthosis was, overall, the most important livestock disease in developing countries.

This paper discusses options for breeding small ruminants, sheep and goats, for resistance to gastrointestinal nematode parasites, specifically strongyle parasites such as *H. contortus*. A precise definition of resistance is given below. Evidence for genetic variation in resistance to *H. contortus* and other nematode parasites will be briefly summarised, options for genetic improvement of resistance will be considered and issues such as potential impacts on animal performance and the likelihood of parasite evolution will be discussed. Typically, these small ruminants will be kept in small-holder production systems, in which security of production is critical to sustainability. It is also likely that many of these communities will have weak infrastructure, limiting the

sophistication of the breeding programmes that can be implemented.

Evidence for genetic variation in nematode resistance

The term disease resistance is often used loosely and generically to cover both resistance to infection as well as resistance to the disease consequences of infection, that is, disease tolerance. Following the terminology of Bishop and Stear (2003), resistance to infection essentially describes the host's ability to interact with and control the lifecycle of the parasite. In the context of nematode infections, this may include the establishment probabilities of ingested larvae, rate and extent of parasite development within the host, parasite mortality and parasite fecundity – and hence faecal egg count (FEC). It is important to note that resistance is a relative term, and complete resistance to nematode infection is unlikely to be ever seen. Disease tolerance is often used to describe a host's ability to withstand pathogenic effects of infection. Resilience is related to tolerance, and describes an animal's ability to maintain performance in the face of a disease challenge.

The ability to breed animals for improved nematode resistance is dependent upon the existence of genetic variation between animals in their resistance to (or tolerance of) such infections and the ability of the breeder to identify and breed from the more resistant animals. Genetic variation in nematode resistance at both the between-breed and within-breed levels has been summarised by Bishop and Morris (2007). In their review, these authors concluded that breed differences in resistance to nematode infections have been well documented, particularly for tropical or sub-tropical sheep facing *H. contortus* challenge. Although many of the published breed comparison studies lack power, a consensus between studies has emerged. For example, in sheep there is ample evidence for the Barbados Blackbelly, St Croix, Florida Native and Gulf Coast Native breeds from the Caribbean and southern United States being relatively resistant, when compared with non-adapted breeds (Baker and Gray, 2004). In India, the Garole breed appears to be relatively resistant compared with other breeds (Nimbkar *et al.*, 2003). In Africa, considerable evidence has demonstrated the favourable resistance and tolerance characteristics of the Red Maasai breed (Baker and Gray, 2004), and this resistance translates into improved performance under many environmental conditions (Baker *et al.*, 2004). Similarly, in goats the West African Dwarf goat shows both trypanotolerance and resistance to nematode infections (Chiejina and Behnke, 2011).

Most within-breed studies of genetic resistance use FEC as the indicator trait for resistance, and significant heritabilities are invariably found, coupled with extensive between-animal variation in FEC (Bishop and Morris, 2007). Most heritabilities for FEC in sheep are generally in the range from 0.2 to 0.4, although values in goats tend to be slightly lower, for example, from 0.1 to 0.35. Importantly, resistance to different strongyle parasites appears to be strongly genetically correlated, perhaps approaching unity (Gruner *et al.*, 2004), and even between

Strongyle and *Nematodirus* FEC, genetic correlations are at least 0.5 (Bishop *et al.*, 2004).

Quantitative trait loci (QTL) studies for nematode resistance, using microsatellite markers, have now been undertaken in many countries (Paterson *et al.*, 1999; Beh *et al.*, 2002; Diez-Tascon *et al.*, 2002; Cockett *et al.*, 2005; Davies *et al.*, 2006; Moreno *et al.*, 2006; Gutiérrez-Gil *et al.*, 2009; Marshall *et al.*, 2009). A conclusion from these published results is that most significant QTL effects tend to be scattered throughout the genome. Only regions on chromosomes 3 (near to the interferon gamma locus) and 20 (within or adjacent to the MHC region) consistently appear significant across studies. Although some QTL appear to have large sizes of effect, caution must be used in interpreting these results, as it is the effects with the largest overestimation bias that will be the most significant.

Attention is now turning to genome-wide association studies using dense single nucleotide polymorphism (SNP) arrays. These studies attempt to either (i) find SNPs in population-wide linkage disequilibrium with mutations with large effects on the phenotype and/or (ii) develop genomic predictors of performance using the entire SNP chip. Initial results from studies of nematode resistance in sheep (e.g. Kemper *et al.*, 2011), as well as other disease conditions in livestock and humans, suggest that resistance tends to be very polygenic, with few SNPs having large effects. This contrasts with QTL studies, where reported family-specific effect sizes are generally larger.

Selection for nematode resistance

Considerable evidence has now accumulated in developed countries that selection in sheep for resistance to nematode parasites, with selection based solely on FEC, is feasible and likely to be successful (Woolaston and Piper, 1996; Morris *et al.*, 1997; Woolaston and Windon, 2001). One of the most spectacular demonstrations of such selection was documented by Kemper *et al.* (2010a). Following selection for reduced FEC in merino sheep after a natural challenge, FEC and worm burdens were ca. 20% of those in an unselected control line, after only 15 years of selection. Further, as indicated by the results of Kemper *et al.* (2010a) and the strong genetic correlation between resistance to difference nematode species (Gruner *et al.*, 2004), selection for resistance to one species will tend to increase resistance to other species. Successful short-term selection for nematode resistance in goats has also been reported (Vagenas *et al.*, 2002). Responses to artificial selection for nematode resistance have yet to be demonstrated in tropical sheep or goat production systems; however, long-term natural selection has produced many breeds that are resistant or tolerant of infection, as described above.

One of the main benefits of genetically improving resistance to nematodes is the epidemiological effect arising from reduced FEC (Bishop and Stear, 1997). Resistant sheep excrete fewer eggs and this ultimately leads to a reduced pasture larval contamination, as more eggs are removed from the pasture, through mortality or ingestion, than are

returned. This reduced pasture larval contamination leads to reduced challenge and lower FEC, and hence a greater apparent response to selection, as well as benefits in performance (Bishop and Stear, 1999). Ultimately, this will benefit all animals grazing the same pasture, not only the genetically more resistant animals. Experimental evidence supporting this concept has been presented by Leathwick *et al.* (2002), Gruner *et al.* (2002) and Williams *et al.* (2010).

SWOT analysis of breeding programmes

In their report to the FAO (Opportunities for Incorporating Genetic Elements into the Management of Farm Animal Diseases: Policy Issues), Bishop *et al.* (2003) identified generic strengths, weaknesses, opportunities and threats for breeding programmes applied to disease resistance under tropical conditions. These may be adapted to the situation of nematode infections as follows:

Strengths

1. Genetic change is permanent
2. Consistency of effect: 'just keeps working'
3. No continued input required once established
4. Prolong/protect the effectiveness of other methods (lifetime)
5. Broad-spectrum effects, that is, increased resistance to one disease can increase resistance to others
6. Adds to diversity of management strategies

Weaknesses

1. Goals of production system may change more quickly than genetic change can be implemented
2. Uncertainty of genetic outcomes in different environments and production systems
3. Need for some level of controlled breeding
4. Cost of measurements and analysis
5. Adds to technologies to be understood and implemented

Opportunities

1. Marketing of disease-resistant stock
2. Infrastructure that can be used for the other purposes, for example, performance recording
3. Mobilise communities for related activities including training and acquiring skills for farm and community management, marketing, politics

Threats

1. Inappropriate stock may become cheap and/or widely available
2. Genetic material may not be owned by local stakeholders
3. Opposition/competition from existing investors in other control options, for example, chemical suppliers

Clearly, a main benefit of breeding for resistance is its sustainability, that is, the fact that it is permanent and continues with little or no intervention once achieved. However, this has to be offset against the complication of applying

what might be quite complex technology in the first instance. However, the infrastructure required to achieve genetic gain can be seen as an opportunity to obtain added value, through gaining of skills and other technical opportunities such as performance recording. An identifiable threat, which has occurred on occasions, is the use of inappropriate livestock, for example, imported animals from Europe or North America that lack adaptation characteristics to local conditions.

Choice of appropriate phenotype

So far, only FEC has been considered as the indicator of relative resistance to nematodes. However, there are several indicator traits that could be considered. These may be classified as follows:

- *Measures of resistance:* FEC, worm burden, worm size and fecundity.
- *Immune response:* Eosinophilia, antibodies such as IgA, IgG and IgM.
- *Measures of impact of infection:* anaemia, pepsinogen or fructosamine concentrations.
- *Resilience:* growth rate and required treatment frequency.

Of these traits, FEC, anaemia and growth rate are obvious goal traits, that is, traits that should be improved. In animals infected with *H. contortus*, anaemia can be easily measured using either packed cell volume (PCV) or Famacha© score, an indicator of anaemia in the eyelid. PCV is heritable in sheep and goats (e.g. Baker *et al.*, 2001; Baker *et al.*, 2003; Mandonnet *et al.*, 2006) and emerging data also demonstrate that Famacha© scores are heritable in sheep (Riley and Van Wyk, 2009). Furthermore, anaemia scores are consistently negatively genetically correlated with FEC and positively correlated with live weight, making definition of selection goals straightforward, that is, decrease FEC and increase PCV and live weight gain.

Considerable work has been carried out looking at the genetic properties of the other mentioned traits, that is, concentrations of various antibodies (Strain *et al.*, 2002; Gutiérrez-Gil *et al.*, 2010; Murphy *et al.*, 2010), eosinophils (Stear *et al.*, 2002; Mandonnet *et al.*, 2006), pepsinogen (Davies *et al.*, 2005; Gutiérrez-Gil *et al.*, 2010) and fructosamine (Stear *et al.*, 2001). All these measurements show desirable properties, such as being moderately to highly heritable and often strongly correlated with goal traits such as FEC or worm burdens (Davies *et al.*, 2005). In fact, the results of Davies *et al.* (2005) suggested that selection indices may rather easily be constructed with a number of additional indicator traits.

However, interpretation of indicator traits that describe animals' immune responses or the impact of disease is complicated by the fact that these traits are a part of a dynamically changing response of the host to the parasite. Thus, they change over time and they are also affected by the previous challenge levels that animals have faced. In a study of longitudinal changes in genetic relationships, Davies (2006) showed that not only did genetic correlations of traits such as IgA or eosinophil concentrations with FEC or worm fecundity change over time, but that often they changed sign between times when lambs presumably had immature

immune responses (e.g. 3 months of age) to when lambs had more mature immune responses (e.g. 6 months). This cautions against their use in breeding programmes, unless their genetic properties are well characterised. Consequently, breeding programmes based on phenotypic measurements in the lamb would more robustly focus on FEC, live weight gain and a measure of anaemia, such as PCV or Famacha© score, as described above. Care must be always taken that phenotypic measurements are truly comparable between animals. For example, the effectiveness of the Famacha© score as an indicator of anaemia will vary between breeds, and its utility may be limited in sheep that are only lightly infected (Moors and Gauly, 2009).

Resistance or resilience?

An issue that is often debated by parasitologists and breeders is whether it is more appropriate to select for resistance or resilience, the latter clearly being a desirable attribute in ruminants. Although resilience is usually thought of as the ability of an animal to maintain performance in the face of parasitic challenge, it has also been defined in terms of anthelmintic treatment requirements (specifically "the age at which a first post-weaning anthelmintic treatment is required to maintain acceptable growth in lambs grazing nematode-contaminated pasture" Morris *et al.*, 2010) and anaemia following *H. contortus* infection (Baker *et al.*, 2003). Long-term selection for decreased treatment requirements has been shown to be successful and was accompanied by an increase in growth rate and a decrease in breech soiling (Morris *et al.*, 2010); however, it was complex to implement under practical conditions and did not improve resistance. Conversely, selection for a combination of resistance and performance should encompass the concept of resilience, and also allow some of the epidemiological benefits of selection described above to be captured. The choice of the optimal trait to select on will often depend on the feasibility of trait recording under practical conditions.

Use of genetic markers

Incorporation of genotype information, using genetic markers, is often argued as a means of making selection quicker and more efficient, avoiding the requirement for animals to be challenged with nematodes. However, this may prove problematic in practice, particularly for sheep or goats raised under tropical conditions. Reasons for this conclusion are briefly explored.

Most reported genetic marker studies for nematode resistance have detected and explored microsatellite-based QTL (Paterson *et al.*, 1999; Beh *et al.*, 2002; Diez-Tascon *et al.*, 2002; Cockett *et al.*, 2005; Davies *et al.*, 2006; Moreno *et al.*, 2006; Gutiérrez-Gil *et al.*, 2009; Marshall *et al.*, 2009). However, results from such studies are often difficult to utilise in breeding programmes for a number of reasons. The primary difficulty is that the QTL are generally detected within families, and the linkage phase of markers with causative mutation(s) is family specific. This places an onerous task on re-establishing linkage phase within each family, and consequently leads to a continued large-scale requirement

for phenotyping. Further, QTL will not be detected in homozygous families. Added to these difficulties are the observations that QTL for nematode resistance generally have small effects, that is, many are required to explain a substantial proportion of the genetic variation, and the technical challenges and costs associated with performing large numbers of microsatellite genotypes. Considerable infrastructure will be required to collect and extract DNA, prepare it for genotyping and perform the actual genotyping. Together, these factors mean that such QTL are unlikely to be sustainably incorporated into breeding programmes.

An alternative to microsatellite-based QTL is the exploitation of SNP associations, that is, SNPs that are associated with favourable phenotypes across an entire population. Because this technique uses SNPs that show population-wide disequilibrium with the causative mutation, or may even be the causative mutation in rare cases, the issue of family-specific linkage phase is avoided. To date, very few SNP association studies have been reported for nematode resistance in sheep or goats, and available evidence suggests that individual SNPs are likely to be associated with very small effects (Kemper *et al.*, 2011). In other words, resistance is somewhat polygenic. Consequently, many SNPs would need to be included in a breeding programme to achieve reasonable genetic progress.

An alternative use of SNPs is in genomic selection. In this technique, all SNPs on an SNP chip, for example, >50 000 SNPs, are used simultaneously to predict the genetic merit of an individual, irrespective of the significance of individual SNPs (Meuwissen *et al.*, 2001). This approach is now widespread in the dairy cattle breeding industry, which is characterised by a large census size but small effective population size, and a cumbersome and time-consuming progeny testing strategy. In such cases, selection accuracies of up to 80% can be achieved in the absence of phenotype information (Daetwyler *et al.*, 2010), once robust genomic prediction equations have been developed. The situation for small ruminants is more challenging. The requirement to genotype and phenotype many thousands of animals in order to develop prediction equations will be difficult to achieve. Further, in many populations, for example, the Merino, effective population sizes are large suggesting that chips of 50 000 SNPs will be too small to achieve adequate accuracy of genotype prediction (Kemper *et al.*, 2011). Lastly, extrapolation of results across distantly related populations is poor (Hayes *et al.*, 2009), with the genetically fragmented nature of sheep and goat breeds making it difficult to use the results on anything other than the population in which they were derived. Therefore, genomic selection, at least with current technologies, is likely to be expensive and logistically difficult to implement in tropical sheep and goats.

In summary, sustainable breeding programmes in sheep and goats for nematode resistance are likely to be based on phenotypic measurements, at least in the short term. Sustainable breeding will require the correct choice of genotype, that is, breed, accompanied by efficient phenotype measurement and parentage recording. At least with current technologies, genetic markers are unlikely to make

a substantial contribution to such breeding programmes under tropical conditions.

Issues associated with nematode resistance

Genetic correlations with performance and genotype by environment interactions

The genetic relationship between performance and resistance to nematodes is often misunderstood (Bishop and Stear, 2003). Incorrect inferences are often drawn from observations such as the fact that locally adapted breeds tend to be small with poor production characteristics, whereas high-performing exotic breeds often have poor disease-resistance characteristics. These breed differences are likely to simply reflect their selection history; it cannot be concluded that they reflect an antagonism between resistance and performance. To deduce such relationships, it would be necessary to perform a within-breed genetic study.

As summarised by Bishop and Stear (2003), genetic relationships between performance and resistance are the outcome of a complex set of factors. Firstly, although infection inevitably compromises performance, the ability of an animal to withstand infection or disease depends on the environment, particularly the protein nutrition available to the animal (Coop and Kyriazakis, 2001). It may also be asserted that the genes controlling resistance *per se* and those influencing performance are generally not associated, that is, they are different genes with different gene variants. Consequently, genetic relationships between resistance and performance may be thought of as the outcome of a balance between two opposing factors: the resources used by the host to fight or protect against infection *v.* the damage caused by infection. If the resources used to protect the host outweigh the benefits of being more resistant, then the relationship will be unfavourable. If the benefits of being resistant, that is, the damage that is avoided, outweigh the costs of achieving resistance, then the relationship will be favourable.

This framework predicts that the genetic relationships of resistance and performance will vary with both the disease and the environment. As resources are improved, for example, better nutrition, then there will be less trade-off and a weaker relationship. Conversely, if the challenge level increases, then the benefits of being resistant increase and a stronger relationship is predicted. This framework also predicts genotype by environment interactions, for example, the ranking of animals on their performance may differ in environments with different challenge levels. This last prediction has been demonstrated in the comparison of Red Maasai (resistant and tolerant of nematode infections) *v.* Dorper sheep (susceptible; Baker *et al.*, 2004). In this comparison, breed differences in performance that were present in the face of strong nematode challenge (favouring the resistant Red Maasai) disappeared in an environment with a low-level challenge.

Sustainability of resistance and worm evolution

A feature of widespread and indiscriminate use of anthelmintics is the evolution of resistance by the nematode population to the specific chemical used for their control.

Such anthelmintic resistance is now widespread (Waller, 1997; Waller, 2003; Jackson *et al.*, 2009). Therefore, an equivalent concern is whether host genetic resistance would similarly breakdown over a period of time, with the nematodes evolving to adapt to the resistant hosts. The apparently polygenic nature of parasite resistance in sheep and goats would suggest that worm evolution is likely to be slower than the evolution of anthelmintic resistance, as worms would have to evolve against many more targets. Further, there is no published evidence for apparently resistant breeds losing their relative advantage in resistance compared with more susceptible breeds. Nevertheless, it is useful to consider the available evidence.

Kemper *et al.* (2009) reported serial passage of two strongyle species, *H. contortus* and *Trichostrongylus colubriformis*, through genetically susceptible and resistant hosts, for many parasite generations. The parasite strains were then tested not only in the host populations within which they were passaged but also in unselected outbred hosts. The experiment did produce some evidence of evolution in the worm populations; essentially, the passaging technique was equivalent to performing a weak selection experiment for fecundity within the parasite population. However, there was no evidence for differential adaptation between the resistant and susceptible hosts.

To make more general predictions on the likelihood of parasite evolution, and to develop a likely time horizon over which such evolution may occur, a predictive framework for parasite evolution was then developed, consisting of interacting models at three levels: disease epidemiology, host genetics and parasite genetics (Kemper, 2010; Kemper *et al.*, 2010b). These models successfully predicted rapid rates of development of anthelmintic resistance. However, they predicted only slow rates of evolution in the parasite in response to resistant hosts. This, coupled with likely fitness costs to the parasite (Jorgensen *et al.*, 1998), leads to the conclusion that even with some, albeit slow, change in parasites subjected to resistant hosts, the advantage in terms of reduced FEC in these hosts is likely to be maintained, at least for many parasite generations. Therefore, selection for resistant hosts can be considered a sustainable control strategy, although it will be most effective when used to complement other control strategies.

Conclusions

Breeding for enhanced resistance to nematode parasite may greatly facilitate and enhance parasite control. In tropical production systems where flock sizes are likely to be small, with diverse production systems and host genotypes, selection on phenotype is likely to be the most feasible option. The first step will be the choice of resistant or tolerant breeds, followed by measurement of traits such as growth rate in the face of challenge, FEC and anaemia. With current technologies, the use of genetic markers is likely to be too expensive and logistically difficult. With a correctly derived selection index and adequate management, selection for enhance resistance to nematodes should improve rather than compromise performance. Further, it is unlikely that the

parasites will evolve to overcome the enhanced host resistance, at least in the foreseeable future.

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